Supplementary information

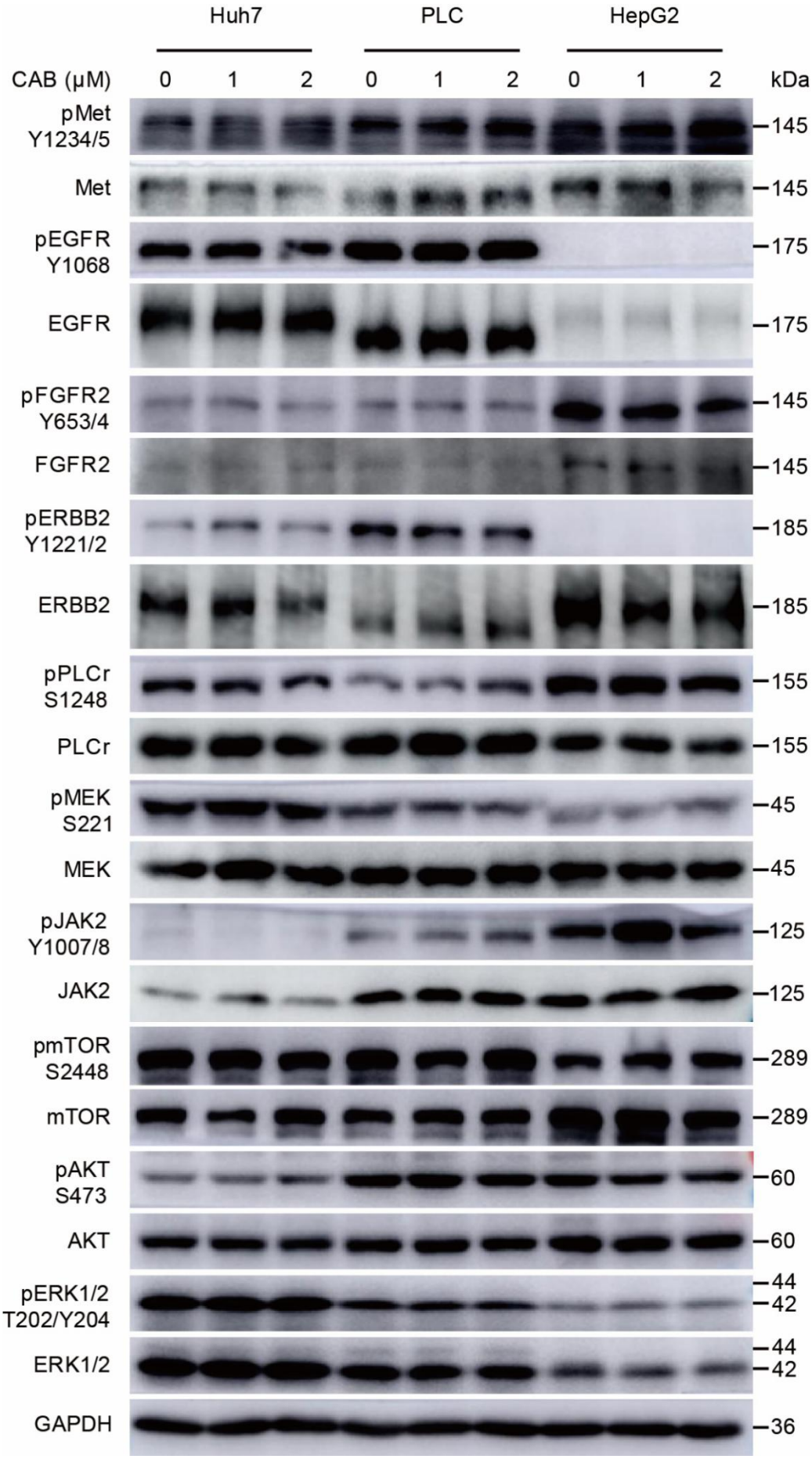
Huh7
PLC
HepG2
CAB (μM)
0
1
2
0
1
2
0
1
2
kDa
pMet Y1234/5
145
Met
145
pEGFR Y1068
175
EGFR
175
pFGFR2 Y653/4
145
FGFR2
145
pERBB2 Y1221/2
185
ERBB2
185
pPLCr S1248
155
PLCr
155
pMEK S221
45
MEK
45
pJAK2 Y1007/8
125
JAK2
125
pmTOR S2448
289
mTOR
289
pAKT S473
60
AKT
60
pERK1/2 T202/Y204
44
42
ERK1/2
44
42
GAPDH
36

Fig. S1 The phosphorylation levels of RTKs are diverse among cMet-low HCC cells. The phosphorylation levels of a panel of RTKs and downstream effectors in cMet-low Huh7, PLC and HepG2 cells treated with cabozantinib (CAB) at the indicated concentrations were analyzed by Western blot analysis.

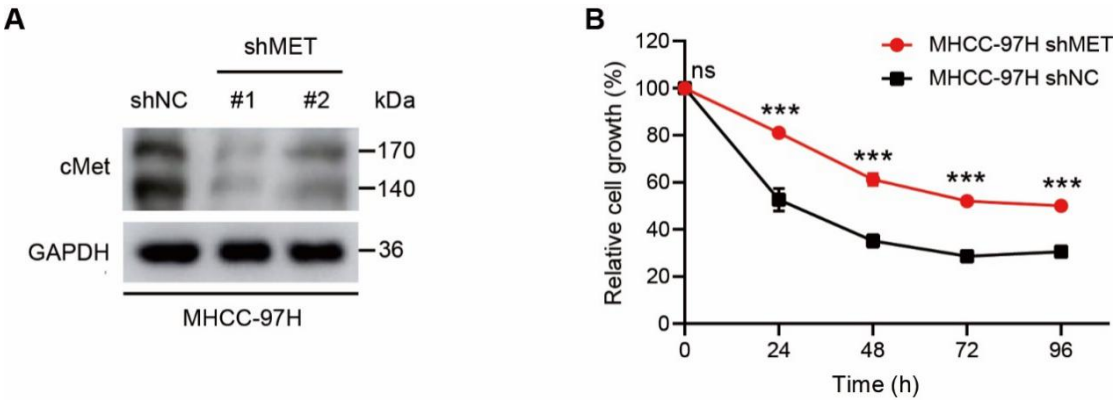

Fig. S2 Knocking down cMet compromises the inhibitory effect of cabozantinib and rapamycin on cMet-high HCC cells. (A) Confirmation of the knockdown efficiency of two cMet shRNAs in MHCC-97H cells determined by Western blot analysis. (B) The proliferation of shMET and shNC MHCC-97H cells treated with cabozantinib (2 μmol/L) and rapamycin (10 nmol/L) for 4 days was measured using CCK8 assay. The significance was determined by two-way ANOVA (Bonferroni post test). Data are shown as the mean ± SD from three biological replicates. ***$P < 0.001$; ns: not significant.

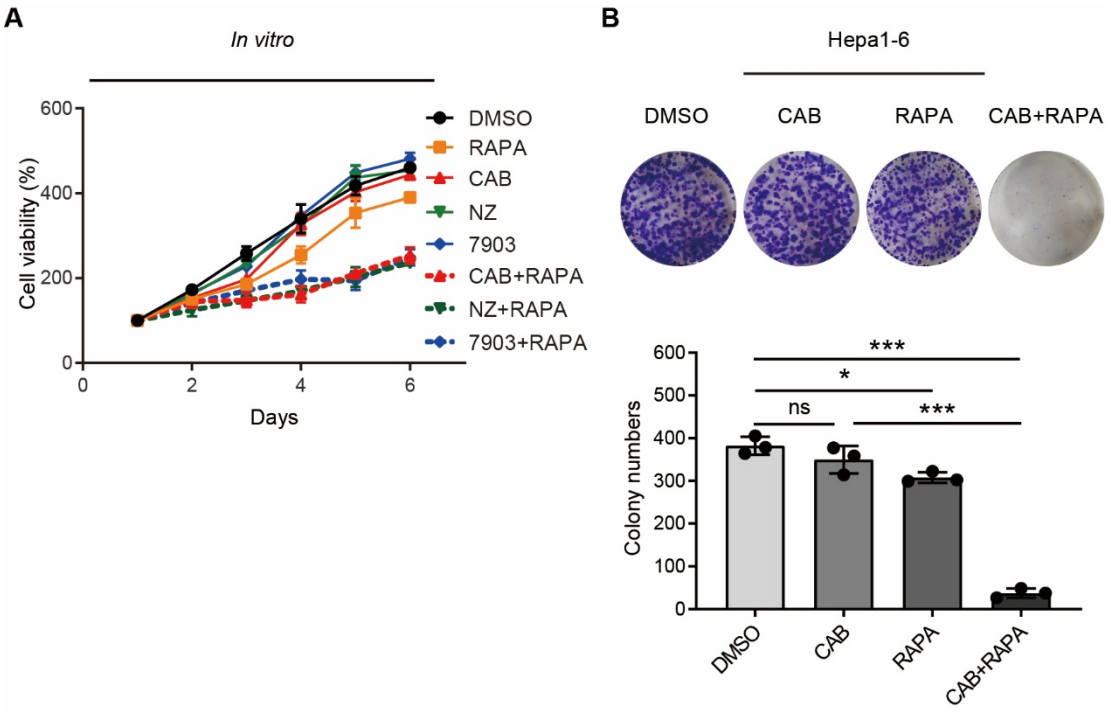

Fig. S3 Rapamycin augments the inhibitory effect of cMet inhibitors on the proliferation and colony formation of Hepa1-6 cells *in vitro*. (A) The growth curve of Hepa1-6 cells treated with indicated inhibitors (rapamycin (RAPA, 10 nmol/L), cabozantinib (CAB, 2 μmol/L), NZ001 (NZ, 2 μmol/L) and PF-04217903 (7903, 2 μmol/L)) alone or in combination for 6 days was determined by CCK8 assay. The significance was determined by two-way ANOVA (Bonferroni post test). (B) The colony formation assay of Hepa1-6 cells treated with cabozantinib (CAB, 2 μmol/L) or in combination with rapamycin (RAPA, 10 nmol/L) was performed. Representative images are shown (upper of B) and the colony number of different groups was calculated (lower of B). The significance was determined by one-way ANOVA (Bonferroni post test). Data are shown as the mean ± SD from three biological replicates. **P* < 0.05; ****P* < 0.001; ns: not significant.

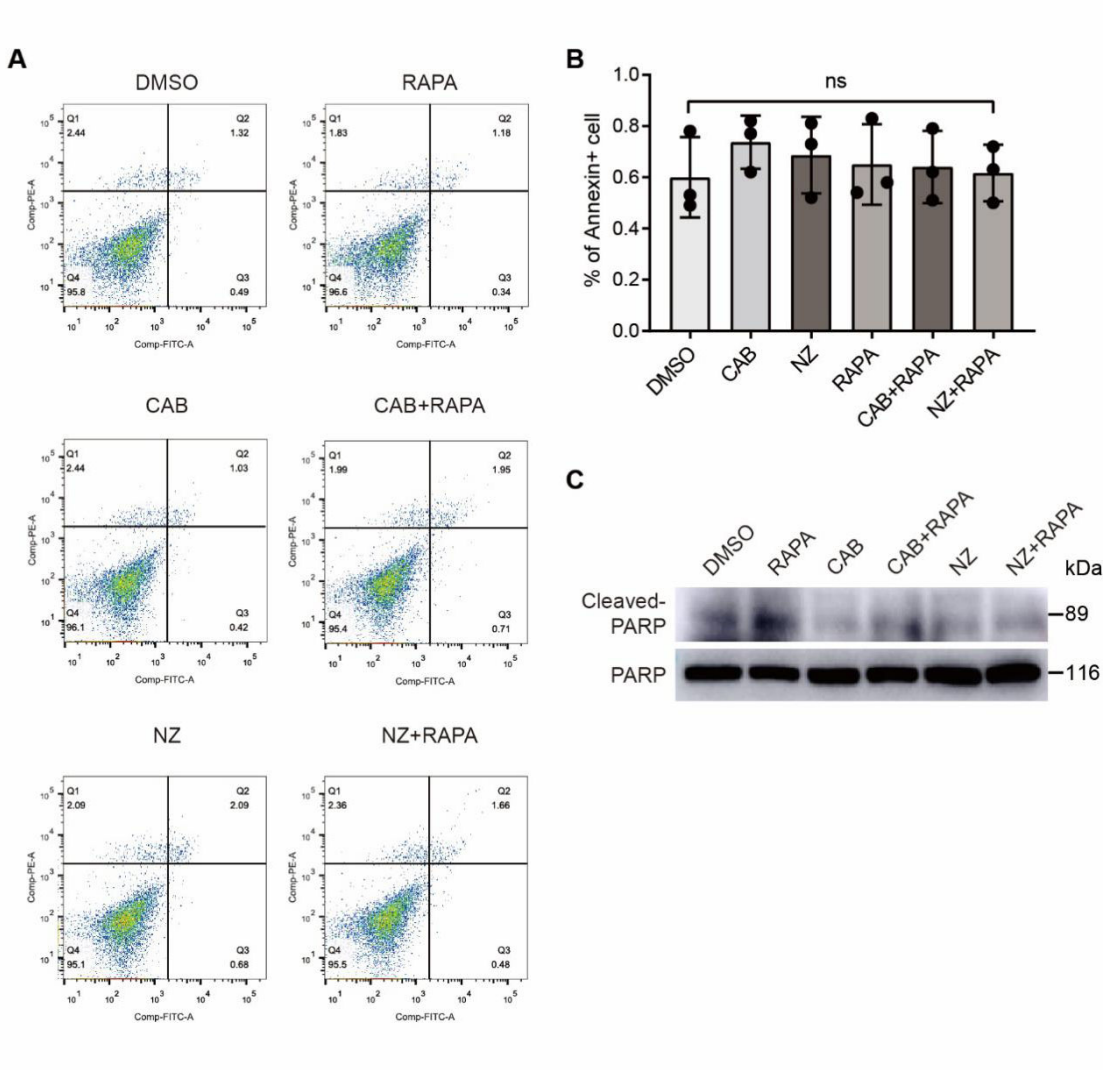

Fig. S4 The combination treatment shows no effect on apoptosis of Huh7 cells. (A, B) Apoptosis assay of Huh7 cells treated with indicated inhibitors (cabozantinib (CAB, 2 μmol/L), NZ001 (NZ, 2 μmol/L) and rapamycin (RAPA, 10 nmol/L)) was conducted with annexin V-FITC/PI staining. Representative images are shown (A) and the percentage of apoptotic (Annexin+) Huh7 cells was calculated (B). For (B), data are shown as the mean ± SD from three biological replicates, and the significance was determined by one-way ANOVA (Bonferroni post test). (C) The expression of cleaved-PARP in Huh7 cells treated with rapamycin (RAPA) and cMet inhibitors (cabozantinib (CAB, 2 μmol/L) or NZ001 (NZ, 2 μmol/L)) alone or in combination was determined by Western blot. ns: not significant.

Table S1 shRNA targeting sequence

Target gene	shRNA number	Sequence
MET	shRNA#1	CAGAATGTCATTCTACATGAG
	shRNA#2	GCCAGCCTGAATGATGACATT